Challenging dogmas in pancreatic surgery: biliary drainage, outcome and beyond
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Endoscopic Ultrasound as Add-On Test after Negative CT: The Optimal Algorithm for Lesion Detection?
ABSTRACT

Background
When clinically suspected a negative computed tomography (CT) does not fully exclude a tumor in the pancreatic head. The accuracy of a diagnostic strategy with conditional endoscopic ultrasound (EUS), serving as add-on test only after negative or inconclusive CT, has not been evaluated.

Methods
Retrospective analysis of tertiary referred patients, who had a suspected pancreatic head lesion without signs of unresectability on CT. We evaluated diagnostic accuracy of EUS after inconclusive CT and EUS after inconclusive or negative CT. We compared results with a single imaging strategy (CT only).

Results
CT detected a solid lesion in 198 (59%) of 335 included patients, of whom 189 (95%) had a (pre)malignant lesion. CT was inconclusive or negative in 137 (41%) patients. In 106 (77%) of them EUS was performed, which was positive in 63 (59%), of whom 53 (84%) had a (pre)malignant lesion. In the 43 cases where EUS did not demonstrate a lesion 10 (23%) had a (pre)malignant lesion. Sensitivity of a strategy with EUS after inconclusive CT was 90%. A strategy with EUS after inconclusive or negative CT resulted in the largest increase of sensitivity compared to CT only (96 vs. 75%, p<0.001).

Conclusions
A diagnostic strategy for detecting solid pancreatic lesions with application of EUS as add-on test after inconclusive or negative CT results in a significant gain of accuracy. Although the likelihood is very low repeat EUS investigations should be planned when both tests are negative, because this does not completely rule out (pre)malignancy.
**INTRODUCTION**

Adenocarcinoma comprise the majority of pancreatic neoplasms and are a leading cause of cancer death in the Western world. Metastatic disease or extensive locoregional ingrowth at the time of presentation precludes a curative surgical treatment in most patients. Early and accurate imaging is a prerequisite to identify potentially resectable lesions, but also avoids unnecessary surgery for incurable, or absent disease. Surveillance programs in well-defined, high-risk groups of patients could enhance the number of potential candidates for surgery.

The most widely available test for the detection and staging of suspected pancreatic and periampullary malignancies is helical contrast-enhanced computed tomography (CT). A meta-analysis, comparing transabdominal ultrasonography (US), CT, and magnetic resonance imaging (MRI) for identifying pancreatic adenocarcinoma and resectability assessment confirmed that helical CT had highest diagnostic accuracy. CT sensitivity was estimated at 91%, which implicates that a negative CT does not rule out a solid pancreatic or periampullary (pre)malignancy.

Endoscopic ultrasonography (EUS) is a technique with superior visualization of the pancreas. Its use in the diagnosis and locoregional staging of suspected pancreatic head tumors has been widely evaluated. Although initially reported as highly accurate, the accuracy of EUS in diagnosing pancreatic cancer appeared to be variable in more recent reports. These discrepancies are largely explained by differences in patient selection and operator experience. Furthermore, CT is widely available, is submerged to ongoing technical improvements and offers the ability to assess distant metastasis. Therefore, EUS is unlikely to replace CT, but rather to serve as an add-on test after a negative CT. Add-on tests can increase the sensitivity of the existing pathway, possibly at the expense of specificity. So far, EUS has not been evaluated for this specific role.

The aim of the present study was to estimate the accuracy of a diagnostic strategy with EUS as add-on test after a negative or inconclusive CT in detection of a solid (pre)malignancy in the pancreatic head.

**METHODS**

**Patients**

The study was performed at the Academic Medical Center, a referral center for treatment of hepatopancreatobiliary diseases. Patients were identified from two prospective databases: the surgery department database, which records data of all explorations for pancreatic diseases, and the endoscopic reports database (Endobase®) of the gastroenterology department, containing all EUS procedures.

We included patients with a clinical suspicion of a solid pancreatic head or periampullary mass (e.g. obstructive jaundice, epigastric pain, weight loss etc., specific laboratory values or transabdominal ultrasound findings), who had no evidence on CT (ref-
ere test) of unresectable disease (distant metastasis or local vascular involvement, defined as tumor surrounding portal or mesenteric vessels for more than 180 degrees of their circumference or an irregular vessel margin). The presence of a biliary stent to relieve obstructive jaundice was not a contraindication for inclusion. Because our hospital serves as a tertiary referral center, the number of patients with unresectable disease is generally low. Exclusion criteria were patients with a cystic tumor, EUS for vascular assessment, EUS for fine-needle aspiration cytology, EUS performed prior to high quality CT, and EUS performed elsewhere. Availability of malignant brush or biopsy obtained by endoscopic retrograde cholangiography in referral centers was another exclusion criterion for the present study, since this was a reason to proceed directly to surgical exploration after CT, without exerting further diagnostics.

In our center no attempts are made to obtain cytological or histological proof of malignancy preoperatively in patients with a pancreatic mass lesion. The decision whether to operate on patients was generally made in multidisciplinary meetings with all clinical and imaging data available.

**Multislice Spiral Computed Tomography**

CT was considered of sufficient quality when a multidetector arterial and portal venous scans were obtained after administration of intravenous contrast with thin slices of 2-3 mm without artefacts. Scans performed in referring hospitals that met these standards were routinely reread by an experienced hepatopancreaticobiliary radiologist. In case of insufficient quality CT examination was repeated. From the CT investigation we recorded (i) tumor size; (ii) presence of infiltration of peripancreatic fat planes (hepatic-duodenal ligament and mesentery); (iii) encasement of the portal or superior mesenteric vein, measured in three categories of circumferential involvement (<90 degrees, 90–180 degrees, >180 degrees); (iv) involvement of the hepatic artery and the superior mesenteric artery; (v) suspected liver metastases; and (vi) distant lymph nodes larger than 1 cm.\(^1\) The radiologist reading the CT images had knowledge of all clinical information.

**Endoscopic Ultrasound**

EUS was performed with a linear scope, or a rotating sector scanner, the Olympus GF-UM20 or GF-UM130 (Olympus Optical, Tokyo, Japan) using frequencies of both 7.5 and 12 MHz, depending on the preference of the endoscopist. In the latter case a water-filled balloon was fitted around the transducer. EUS examinations were almost exclusively performed by two gastroenterologists (M.J.B., P.F.), experienced in endoscopic procedures for pancreatic diseases. At the time of the EUS investigation the attending endoscopist was aware of the clinical information and the CT findings.

**Reference Standard**

A (pre)malignancy was defined as pathology proven (after surgical exploration) pancreatic, ampullary or distal common bile duct adenocarcinoma, villous adenoma, cystic tumor with malignant potential (intraductal papillary mucinous neoplasia,
mucinous cyst, solid and papillary epithelial neoplasm (Hamoudi), renal cell carcinoma metastasis, neuroendocrine tumor or death due to disease (biopsy-proven) at follow-up in case no exploration was carried out. Benign outcome was defined as pathology proven (after surgical exploration), focal chronic pancreatitis or cholangitis, or disease free survival of at least 12 months of follow-up in case no exploration was performed.

Data Interpretation and Statistical Analysis
Results of CT and EUS were classified as negative, inconclusive, or positive. We defined results of imaging to be inconclusive if no radiological diagnosis was made, i.e. no visualization of the mass, but only one or more of the following ‘secondary signs’ of a tumor were present: an inhomogeneous pancreatic head, enlarged pancreatic head, common bile duct (CBD) and/or pancreatic duct (PD) dilatation, CBD or duodenal wall thickening.

We compared three different imaging strategies for detecting a solid (pre)malignant lesion; a CT only strategy, EUS if CT inconclusive, and EUS if CT negative or inconclusive. For the different strategies sensitivity and specificity were calculated by comparing the results of the strategy with the final pathological or follow-up diagnosis. We calculated the percentage of missed cases (1-sensitivity), and the percentage of false positives (1-positive predictive value). The accuracy of the strategies was plotted in a receiver operator characteristics (ROC) space. The difference in accuracy of strategies was calculated by direct comparison of the positive and negative likelihood ratios (LRs) of a CT only and EUS if CT negative or inconclusive strategy, as described by Macaskill.\textsuperscript{15} The threshold for statistical significance was defined as a $P$-value <0.05. All analyses were carried out using SPSS version 17.0.1.

RESULTS

Patient Characteristics
A series of 587 patients, referred between April 2001 and June 2007, was evaluated. After applying the inclusion criteria data from 335 patients could be analyzed for the present study, for we had to exclude 252 patients (101 malignant brush or biopsy, 66 EUS performed prior to CT, 54 cystic tumor on CT, 15 referral CT of inferior quality, 13 EUS for vascular assessment, 2 EUS performed elsewhere, 1 EUS technical failure).

Table 1 displays clinical-pathological characteristics. Pancreatic and periampullary adenocarcinoma were grouped, since differentiation by tumor origin for those who did not undergo resection is generally not possible on tumor biopsies or frozen section alone. Of the 335 patients, 294 (88%) underwent surgical exploration. The median follow-up of patients who did not undergo surgery was 34 (interquartile range [IQR] 17-53) months. The median time from CT to surgical exploration was 56 (IQR 41-77) days. Interval between CT and EUS was 19 (IQR 10-32) days. No adverse events had occurred after either test.
Table 1: Demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>(N=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean – yr</td>
<td>62±11.6</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>126 (38)</td>
</tr>
<tr>
<td>Reported symptoms</td>
<td></td>
</tr>
<tr>
<td>Weight loss – no. (%)</td>
<td>202 (60)</td>
</tr>
<tr>
<td>Weight loss – median kg. (IQR)</td>
<td>5 (3-10)</td>
</tr>
<tr>
<td>Epigastric pain – no. (%)</td>
<td>110 (33)</td>
</tr>
<tr>
<td>Obstructive jaundice – no. (%)</td>
<td>261 (78)</td>
</tr>
<tr>
<td>Recent onset diabetes – no. (%)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>History of (chronic) pancreatitis – no. (%)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>PBD via ERC/PTC – no. (%)</td>
<td>239 (71)</td>
</tr>
<tr>
<td>Underlying pathology – no. (%)*</td>
<td></td>
</tr>
<tr>
<td>Pancreatic/periampullary adenocarcinoma</td>
<td>250 (75)</td>
</tr>
<tr>
<td>Chronic pancreatitis / cholangitis</td>
<td>37 (11)</td>
</tr>
<tr>
<td>No abnormality</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Cystic tumor</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Ampullary or duodenal villous adenoma</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Total malignant</td>
<td>277 (83)</td>
</tr>
</tbody>
</table>

Plus-minus values are means ±SD. IQR denotes interquartile range.
CI confidence interval. PBD preoperative biliary drainage.
ERC endoscopic retrograde cholangiography. PTC percutaneous transhepatic cholangiography.
* Diagnosed during surgery with frozen section (when not resected), at pathological investigation (after resection) or with (endoscopic) biopsies in cases where surgery was deferred, or during follow-up.

Figure 1: Flowchart of study population with test results for different strategies (CT, CT+EUS).
**Patient Flow and Treatment Outcome**

Figure 1 shows the flowchart of the study group with test results. We evaluated 166 (49.6%) internal and 169 (50.4%) external CT-scans from referral centers. CT detected a solid lesion in 198 patients (59%), was inconclusive in 96 (29%), and negative in 41 patients (12%). EUS was performed in 71 patients with an inconclusive CT and in 35 with a negative CT (total 106), while 31 cases proceeded directly to surgical exploration after negative or inconclusive CT. Median tumor size on CT (positive test) was 2.5 centimeter (IQR 2.0-3.5), median tumor size on EUS (positive EUS test) was 1.8 (IQR 1.4-2.3).

Table 2 shows treatment and pathological variables of groups discerned by CT result. Patients that had a positive CT had the highest rates of confirmed (pre)malignant lesions, whereas patients with a negative CT had the lowest rates, but not zero. Patients with a positive CT also had the highest rate of pancreatic or periampullary adenocarcinoma with an associated higher rate of residual tumor at the resection margin (R1) compared to negative or inconclusive CT. A conservative treatment approach was only followed in 4% of patients with positive CT, while almost half of patients with negative CT did not undergo surgery, but close surveillance.

Table 2  
Treatment and pathological outcome according to patient flow with respect to CT result.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CT positive</th>
<th>CT inconclusive</th>
<th>CT negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection– no. (%)</td>
<td>98 (59)</td>
<td>58 (60)</td>
<td>18 (43)</td>
</tr>
<tr>
<td>Palliative bypass procedure or exploration– no. (%)</td>
<td>92 (47)</td>
<td>22 (23)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>No surgery– no. (%)</td>
<td>8 (4)</td>
<td>16 (17)</td>
<td>17 (42)</td>
</tr>
<tr>
<td>Pathological variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pre)malignant lesion– no. (%)</td>
<td>189 (96)</td>
<td>66 (69)</td>
<td>22 (54)</td>
</tr>
<tr>
<td>Pancreatic or periampullary adenocarcinoma– no. (%)</td>
<td>163 (82)</td>
<td>62 (65)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>Other diagnosis– no. (%)</td>
<td>35 (18)</td>
<td>34 (35)</td>
<td>25 (61)</td>
</tr>
<tr>
<td>Microscopically residual disease (R1)– no. (%)*</td>
<td>25 (35)</td>
<td>9 (23)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

* figures applicable to resected pancreatic or periampullary adenocarcinoma.

**Diagnostic Accuracy**

Of the 106 (59%) patients who underwent EUS after inconclusive or negative CT EUS was positive in 63 (46 patients after inconclusive, 17 after negative CT) of whom 53 (77%) had a (pre)malignant lesion (Figure 1). False positive EUS conclusions were focal chronic pancreatitis (n=7), and possible (pre)malignancy (n=3). The latter 3 underwent surveillance with repeated EUS and had complete resolution of symptoms. Of the 43 patients in whom EUS was negative (25 after inconclusive CT, 18 after negative CT) 10 patients still appeared to have a (pre)malignant lesion. False negative EUS conclusions were chronic pancreatitis (n=5), no pathology (n=3), and
inconclusive arguments for (pre)malignancy ($n=8$). Among the 43 patients with a negative EUS, 16 had a biliary stent in place at the time of investigation and 29 did not. The false negative EUS conclusion rate was higher in the group with biliary stent compared to those without, 43% (6/16) versus 14% (4/29) respectively ($P \text{ 0.04}$).

**Table 3** Diagnostic accuracy of each imaging strategy for solid pancreatic or periampullary (pre)malignancy. Percentages (with 95% confidence intervals for sensitivity and specificity) and absolute numbers are given.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Sensitivity %</th>
<th>Specitivity %</th>
<th>Missed cases</th>
<th>False positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single imaging strategy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Computed tomography in all patients</td>
<td>0.75 (0.70-0.80)</td>
<td>0.83 (0.72-0.93)</td>
<td>43</td>
<td>0.25 63/252 0.05 9/198</td>
</tr>
<tr>
<td>Conditional strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT in all patients; EUS only</td>
<td>0.90 (0.86-0.94)</td>
<td>0.67 (0.55-0.80)</td>
<td>35</td>
<td>0.10 25/252 0.07 17/244</td>
</tr>
<tr>
<td>CT in all patients; EUS if CT</td>
<td>0.96 (0.94-0.98)</td>
<td>0.63 (0.50-0.77)</td>
<td>33</td>
<td>0.04 10/252 0.07 19/261</td>
</tr>
</tbody>
</table>

**Figure 2** Sensitivity and 1-specificity for a CT-only strategy (open triangle), EUS if CT inconclusive strategy (closed triangle), and a EUS if CT negative or inconclusive strategy (closed square) are shown in a ROC plot.
Table 3 shows the diagnostic accuracy results for a CT only and for the CT with conditional EUS strategy. Figure 2 shows these results in a receiver operating characteristics space. Application of EUS after an inconclusive CT result had a sensitivity of 0.90 (95% CI: 0.86-0.94) versus 0.75 (95% CI: 0.70-0.80) for CT only, while specificity was 0.67 (95% CI: 0.55-0.80) versus 0.83 (95% CI: 0.72-0.91), respectively. This conditional strategy would result in a significantly lower number of missed (pre) malignancies compared with CT only: 10% versus 25%. Application of EUS after a negative or inconclusive CT would further increase the sensitivity to 0.96 (95% CI: 0.94-0.98), significantly better compared to CT only (P<0.001), and reduce the number of missed diagnoses to 4%. The positive likelihood ratio of CT plus EUS (after negative or inconclusive CT) strategy was 2.63 (95% CI: 1.84-3.76) versus 4.33 (95% CI: 2.38-7.88) for CT only, the negative likelihood ratio was 0.06 (95% CI: 0.03-0.12) versus 0.30 (95% CI: 0.24-0.39).

DISCUSSION

The aim of a diagnostic test is differentiating patients with disease from those without. Its implications depend on the target condition and treatment consequences of a positive test. In case of pancreatic cancer this implicates not withholding a potentially curative resection from eligible patients, but also sparing those without disease a futile laparotomy with associated morbidity. The present study demonstrates that using EUS as add-on test after negative or inconclusive CT in the diagnostic algorithm for detection of a solid (pre)malignancy in the pancreatic head results in a significant gain of diagnostic accuracy.

Earlier studies reported an advantage of EUS over CT and MRI in diagnosing and staging pancreatic tumors for its high accuracy. Some studies have even argued to use EUS as the initial modality in the diagnostic algorithm. More recent studies have dampened down these expectations because of variable results from studies comparing CT and EUS. The likelihood of publication bias, which usually accompanies the introduction of any new technology that challenges established procedures, might explain the previously reported high success rates of EUS. The accuracy of EUS also appeared to be significantly lower when examiners were blinded to clinical information and previous test outcomes. In this paper we investigated the use of EUS as add-on test, i.e. an extra test positioned after an existing diagnostic pathway, in this case in a subgroup of patients with a negative CT. We evaluated the added value of EUS, rather than expressing accuracy in terms of level of agreement with CT, as was done in previous studies. Pursuing proper blinding to either test for fair comparison is not an issue in our study design.

We defined the added value of EUS to the diagnostic algorithm for suspected pancreatic head tumors with respect to lesion detection. We have not investigated the role of EUS in staging disease. Prospectively established criteria for resectability with respect to graded vascular invasion exist for CT, but not for EUS. In fact, EUS is
known to be unreliable for assessment of tumor involvement of the superior mesenteric artery. The value of EUS-guided fine-needle aspiration in the preoperative algorithm is limited; microscopic involvement of local nodes is not a contraindication for surgical exploration. In our center only suspicious distant para-aortal nodes prompt for further investigation. Histology to confirm diagnosis of the primary, potentially resectable lesion is not indicated, as malignancy cannot be ruled out with adequate reliability in case of a negative test result.27

The accuracy of a diagnostic test varies with disease prevalence in the population that is under study.28 The prevalence, in turn, varies with differences in patient spectrum and referral filter. A general awareness of these characteristics is mandatory for proper translation of study results into local clinical practice. In this study we included a cohort of patients referred for diagnosis and treatment for a suspected solid pancreatic head tumor. Although we excluded certain conditions (e.g. cystic lesions, positive brush cytology) we consider the patient spectrum to be a realistic representation of our tertiary clinical practice. Narrow patient inclusion could limit test challenge with a test that may seem to perform better due to an artificially raised prevalence of the target condition in the study population.29 Furthermore, such a post-hoc analysis does not accurately reflect the preoperative clinical situation, when making the right diagnosis is most difficult.

Test accuracy also depends on severity of disease at presentation. The best EUS results for pancreatic and esophageal cancer have been reported in series with a high number of cases with advanced disease stages (T3/4).24,30-32 One might question whether these advanced lesions would not already have been detected by CT. Lesions detected by CT likely represent advanced cases, illustrated in our series by a higher incidence of unresectable lesions and lower rates of tumor-free resection margins, compared to patients with inconclusive or negative CT. This also explains a higher positive likelihood ratio for the CT only strategy; when the test is positive chances are highest for (pre)malignancy. With respect to a CT with EUS strategy, this resulted in a better negative likelihood ratio; when both tests are negative chances are lowest for (pre)malignancy. The initial sensitivity of 71% of CT in lesion detection in the present series is somewhat lower compared to the reported sensitivity of helical CT in a meta-analysis.5 An explanation could be that in the present tertiary referral series the proportion of unresectable (i.e. advanced) cases was relatively low compared to the meta-analysis, thus lowering the detection rate.

The study was performed in a tertiary, high volume center with a relatively high number of potential resectable cases. Concerning the latter, one could propose that the diagnostic work-up of these patients, including EUS, should be performed in an expert center. The relation between volume and quality of outcome is well established and widely recognized.33,34 The fact that the presence of a biliary stent seems to interfere with image quality in this series, both on CT and EUS, has been noticed by others too.35 Biliary stenting contributes to local inflammation and obscures CT and EUS visualization. Therefore, EUS should be performed only after adequate CT imaging, and before biliary drainage. In our tertiary referral population the rate of
biliary stenting was 71%. Considering the fact that biliary stenting to attempt preoperative biliary drainage (PBD) now indisputably has been demonstrated to be associated with unacceptable high morbidity such high biliary stenting rates are likely to decline. Thus, lower rates of PBD could further increase EUS accuracy.

The primary goal of our study was to evaluate the accuracy of a diagnostic strategy using CT as the primary imaging modality with EUS as add-on test in CT negative or inconclusive cases only. Despite both tests being negative in 43 patients, 17 cases proceeded to surgical exploration, suggesting a discrepancy in the recognition of EUS results and clinical decision making. Possibly the fear of withholding a patient a potentially curative treatment in case of an obscure lesion explains this observation. Repeat EUS investigations after an initial negative result might preclude an unnecessary laparotomy. Although it was not the aim of our study one may hypothesize that EUS for lesion detection is not necessary after a positive CT considering the very high positive malignancy likelihood.

Some potential limitations of our study have to be acknowledged. The number of patients with negative or inconclusive CT that underwent EUS was relatively small. Data had to be collected retrospectively, the diagnostic and treatment considerations in individual cases could not always be fully reconstructed, and protocol adherence was not monitored. The reference standard was based on a variety of sources. A number of patients had benign disease, for which an event-free follow-up of twelve months was considered confirmative.

In conclusion, we demonstrated that EUS as add-on test after negative or inconclusive CT for detection of a solid pancreatic or periampullary (pre)malignancy provides a significant gain of accuracy, but that a negative EUS after a negative CT does not completely rule out (pre)malignancy. This is the first study that evaluates and validates the optimal diagnostic algorithm for solid pancreatic head lesion detection. Future studies should externally validate these results, and might also address cost-effectiveness of this strategy.
REFERENCE LIST


